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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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20306	7590	09/24/2004	EXAMINER	
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP			MORAN, MARJORIE A	
300 S. WACKER DRIVE			ART UNIT	
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CHICAGO, IL 60606			1631	

DATE MAILED: 09/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/755,779	Applicant(s) ZEMBOWER ET AL.	
	Examiner Marjorie A. Moran	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) 26-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☒ Claim(s) 25 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 January 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>12/20/01</u> . | 6) <input type="checkbox"/> Other: _____ |

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-25 in the reply filed on 7/6/04 is acknowledged. The traversal is on the ground(s) that the claims are directed to similar methods of optimizing crystallization, which would not require a separate search or pose a serious search burden on the examiner. In addition, applicant argues that the claims are generally drawn to methods for optimizing a "chemical process", therefore restriction detracts from the unity of the invention. This is not found persuasive because as admitted by applicant on pages 2-3 of the response, the method of Group I starts with a step of identifying variables which affect crystallization whereas the method of Group II begins with a step of identifying variables which affect chiral resolution. A solvent which affects chirality is not necessarily one which affects crystallization; e.g. chirality is often dependent on the TYPE of salt and the kinds of solvents whereas crystallization can occur in the presence of any (or no) salt, any (or no) organic solvent, etc., and is generally dependent on the relative *concentration* of both the protein to be crystallized and the various elements in the crystallization buffer. Applicant further admits on pages 2-3 of the response that in Group I, crystals are analyzed whereas in Group II, the magnitude of chiral resolution is analyzed. One may certainly analyze a crystal without any determination of chirality or amount of enantiomers present in a mixture. In addition, the examiner's search for the method of Group I confirms that a search for a method to optimize crystallization is NOT coextensive with a search to optimize chiral resolution. It is noted that a search for any single group requires a search of both nonpatent literature and foreign patents, as well

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as a search of US patents and publications. For the reasons set forth above and previously set forth, the examiner maintains that the Groups are separate and distinct and that a search for both Groups would pose a serious burden.

The arguments with regard to unity of invention are moot as the instant application is a US application, therefore unity of invention rules applied to cases filed under 35 USC 371 do not apply.

The requirement is still deemed proper and is therefore made FINAL.

Claims 26-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/6/04.

An action on the merits of elected claims 1-25 follows.

Priority

The instant application is a continuation in part of US 09/443,987, filed 11/19/1999. '987 fails to provide adequate support under 35 U.S.C. 112 for claims 1-25 of this application because the priority application fails to disclose anything with regard to crystallization. The specification and claims of '987 are directed to determining optimum conditions for a chemical reaction, in particular for chemical synthesis (see e.g. page 13 and claim 1), but are silent with regard to any method of crystallization or,

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in particular, any method of optimizing crystallization. Neither the specification nor claims of '987 teach or recite identifying variables which affect crystallization nor any steps of analyzing crystals. A general method of determining optimal conditions for a *chemical reaction* is not support for a method of optimizing *crystallization*, therefore priority to the '987 application is not granted and the instant claims are accorded priority only to the filing date of the instant application, of 05 January 2001.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the handwritten notations on Figures 3 and 5D are illegible.

Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Information Disclosure Statement

The information disclosure statement filed 12/18/01 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because reference 17 (Advanced Chem Tech) lacks a date of publication and an author's name. It has been placed in the application file, but all the information referred to therein has not been considered as to the merits. Only the initialed references have been considered. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for

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purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Objections

Claim 25 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 23. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 22 are directed to a method for optimizing crystallization, and recites steps of choosing conditions, crystallizing, performing statistical analysis, and generating suggestions for future experiments, but fail to recite any step of actually optimizing crystallization or for choosing optimal crystallization conditions. The generation step of claim 1 is merely one of suggesting parameters for future

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experiments and is not limited to suggesting optimal or improved parameters, but could in fact, result in a suggestion for parameters which result in less than optimal crystallization (e.g. higher "purity" but lower yield, or higher yield but slower time of crystallization), depending on the operator's definition of "optimal". The generation step of claim 22 recites choosing parameters "based on statistical analysis" in order to optimize crystallization, but does not actually recite a step of optimizing crystallization of a target molecule. As it is unclear whether the methods are actually directed to *optimizing* crystallization of a *target molecule*, the claims are indefinite.

Claim 9 recites the limitation "the range of values" in line 3. There is insufficient antecedent basis for this limitation in the claims, therefore claim 9 is indefinite.

The term "most favorable" in claim 19 is a relative term which renders the claim indefinite. The term "most favorable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. As one skilled in the art would not know the metes and bounds intended by applicant for a "most favorable" crystallization, claim 19 is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 and 16-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over WARD et al. (Lab. Rob. Automation (1989) vol. 1, no. 3, pp. 157-176), MORRIS et al. (Biotechniques (1989) vol. 7, no. 5, pp. 522-527) and FLAVIN et al. (US 6,175,816, filed 5/23/1997).

Claim 1 recites a method of optimizing crystallization of a target molecule by identifying variables which affect crystallization, choosing experimental tests (presumably comprising variables), wherein the tests comprise values for the identified variables, providing wells, assigning each of the experimental tests to a particular well,

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dispensing reagents, solvents, and the target molecule into the wells according to the chosen test conditions (as interpreted by the examiner), allowing crystallization to occur in the wells, analyzing crystals in the wells, performing a computer-implemented statistical analysis of the crystals which analysis comprise at least one of the identified variables and the crystal analysis, and generating, via the computer, suggested parameters for future experiments based on the statistical analysis. Claims 2-8 further limit the variables. Claim 9 limits the method to one wherein variables are chosen randomly. Claims 10-18 further limit the crystal analysis. Claim 19 limits the statistical analysis to determination of a "most favorable" crystallization "based on" yield. Claims 20-21 limit the statistical analysis to graphical description, specifically to generation of multivariable contour maps. Claim 22 recites a method similar to claim 1 wherein range of values for variables is determined, and a new range suggested based on the analysis. Claims 23 and 25 limit the new range to be narrower than the original range. Claim 24 limits the values to be chosen randomly.

WARD teaches a method of determining optimal conditions for crystal growth of proteins in a multiwell tray (pp. 157-158) wherein variables which affect crystallization are identified, values (differing concentrations and/or volumes) are assigned to those variables, experimental tests using the values are designed, and solvents and reagents are dispensed into individual wells according to the experimental design (p. 167, right column- p. 169). WARD teaches that variables to be considered are buffers, precipitating agents, ionic strength, temperature, pH, and protein concentration (p. 158). WARD teaches image and statistical processing of the results of his experiments (p.

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172). WARD teaches that his crystal analysis includes analyzing for other compounds (p. 172), determination of size (p. 173), and visual inspection (p. 174). WARD teaches that a desired goal of his method is to automatically generate suggested parameters for future experiments based on analysis of experimental results (p. 174), but does not specifically teach such a step in his method. WARD does not teach graphical analysis or yield determination.

MORRIS teaches that parameters to consider in crystallization include nature of the precipitating agent (i.e. choice of solvent), reagent concentration, temperature, pH, and presence or absence of ligands (pp. 522-523). MORRIS teaches that ranges of values may be chosen (Figures 4 and 5). MORRIS also teaches a desired goal of automatically generating suggestions for future experiments (p. 526), but does not specifically teach such a step.

FLAVIN teaches a method for optimizing chemical processes using statistical methods wherein a computer automatically designs experiments for further investigation until optimized conditions are found (abstract and col. 5, lines 14-30). FLAVIN's automated system is similar in design to that of WARD (see col. 5, line 45-col. 6, line 5). Further, FLAVIN teaches that his statistical method may be used to optimize processes having multiple parameters and for designing experiments with multiple variables (col. 7, lines 43-47). FLAVIN teaches that his analysis may be graphical, specifically in the form of multivariable contour maps (col. 7, lines 30-35), and teaches that parameters to be considered include temperature, time, concentration, and yield (col. 7, lines 26-30).

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It would have been obvious to one of ordinary skill in the art at the time of invention to have included the parameters of MORRIS in the method for determining optimal crystallization conditions of WARD where the motivation would have been to optimize commonly used crystallization parameters, as taught by MORRIS (p. 522). It would further have been obvious to have included the statistical analysis and automatic generation of future experimental parameters of FLAVIN in the method of WARD and MORRIS where the motivation would have been to accomplish the desired goals taught by both WARD and MORRIS. One skilled in the art would reasonably have expected success in combining the statistical analysis and automatic generation of future experimental parameters of FLAVIN with the automated crystallization experiments of WARD and MORRIS because all of WARD, MORRIS and FLAVIN teach automated reactions using a similar device, all teach determination of optimal reaction conditions, and all teach inclusion of similar parameters in their methods.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over WARD et al. (Lab. Rob. Automation (1989) vol. 1, no. 3, pp. 157-176), MORRIS et al. (Biotechniques (1989) vol. 7, no. 5, pp. 522-527) and FLAVIN et al. (US 6,175,816, filed 5/23/1997) as applied to claims 1-14 and 16-21 above, and further in view of the KAHDZHI et al. (US 4,024,013).

Claim 1 recites a method of optimizing crystallization of a target molecule, as set forth above. Claim 15 limits a step of analysis to determining quality of crystals by determining the color of the crystals formed.

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WARD, MORRIS, and FLAVIN makes obvious a method of optimizing crystallization of a target molecule by automatically generating parameters for future experiments, as set forth above. WARD teaches analysis of quality by determining size of crystals, as set forth above, but none of WARD, MORRIS or FLAVIN teach determining crystal color.

KHADZHI teaches analysis of color in a method of crystallization (col. 2, lines 29-49).

It would have been obvious to one of ordinary skill in the art at the time of invention to have included color as a determinant of optimal crystallization, as taught by KHADZHI, in the method of WARD, MORRIS, and FLAVIN, where the motivation would have been to produce crystals with desired/optimal properties, as taught by KHADZHI. One of skill in the art would reasonably have expected success in including the color determination of KHADZHI in the method of WARD, MORRIS and FLAVIN because, although KHADZHI teaches crystallization of a mineral whereas WARD and MORRIS teach crystallization of proteins, all teach similar methods of crystallization and determination of conditions to produce a best or optimal product using similar variables (e.g. temperature, concentration of reagents, addition of crystallization "partners", etc.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571)

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272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
9/20/04